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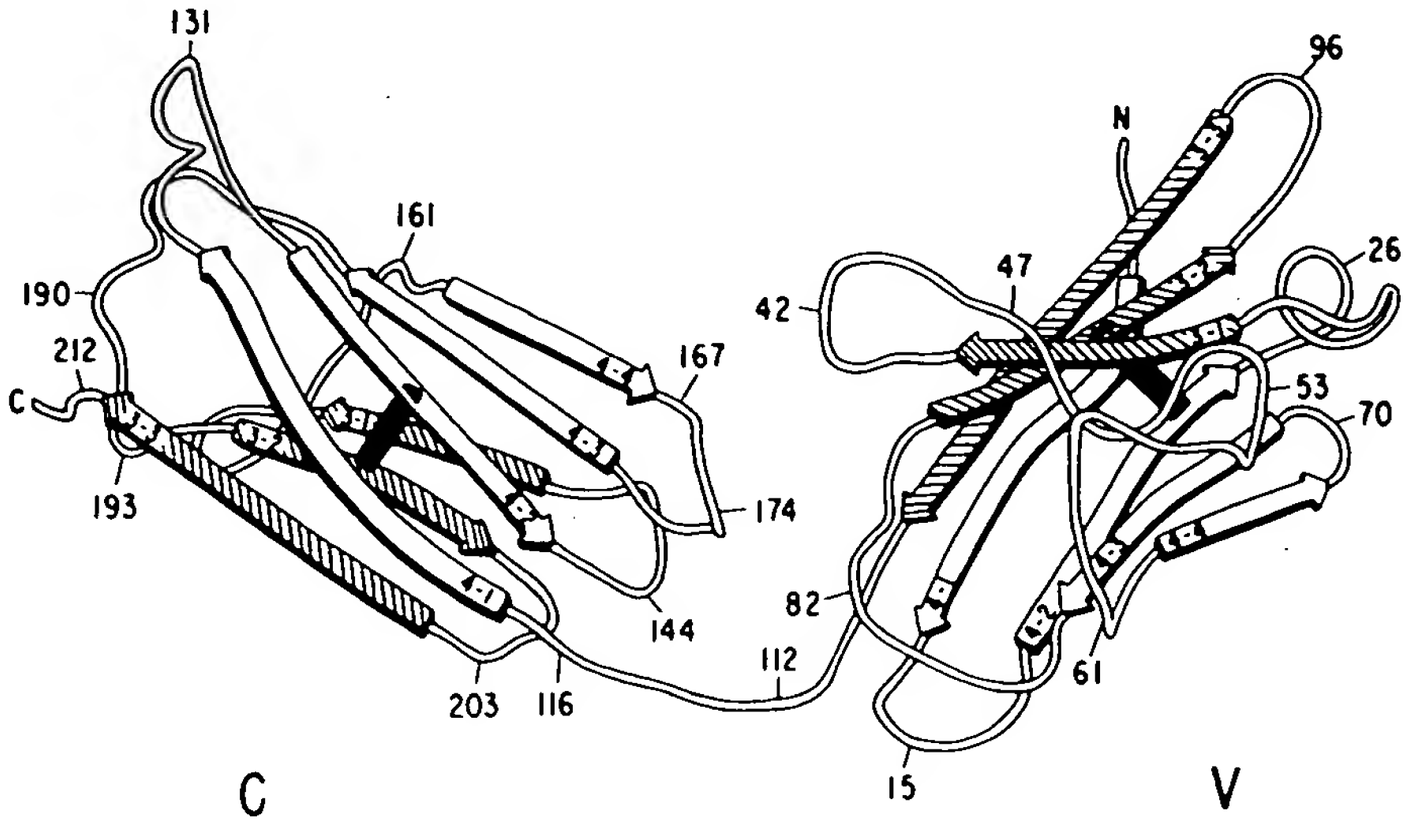

FIG. 5. Schematic drawing of the V and C domains of a light chain. The β strands participating in the antiparallel β-pleated sheets of each domain are represented as arrows. The β strands of the three-stranded sheets are shaded, whereas those in the four-stranded sheets are white. The β strands are numbered according to the scheme of Edmundson. The intradomain disulfide bonds are represented as black bars. Selected amino acids are numbered, with position 1 as the N terminus. (Reprinted with permission from Edmundson AB, Ely KR, Abola EE, Schiffer M, Panagiotopoulous N. Rotational allomerism and divergent evolution of domains in immunoglobulin light chains. *Biochemistry* 1975;14:3953–3961.)

gens of foreign, potentially pathogenic, agents while ignoring antigens associated with the host's own tissues. The mechanisms ensuring this failure to respond to self-antigens are now recognized to be complex and to involve a series of strategies. Chief among them appears to be elimination of cells capable of self-reactivity or the inactivation of such cells. The encounter of immature, naive B cells with antigens with repetitive epitopes capable of cross-linkage of membrane Ig can lead to elimination of the B cells, particularly if no T-cell help is provided at the time of the encounter. This elimination of potentially self-reactive cells is often referred to as clonal elimination. However, there are many self-antigens that are not encountered by the developing B-cell population or that do not have the capacity to cross-link B-cell receptors to a sufficient degree to elicit the clonal elimination process. Such cells, even when mature, may nonetheless be inactivated through a process that involves cross-linkage of receptors without the receipt of critical costimulatory signals. These inactivated cells may be retained in the body but are unresponsive to antigen and are referred to as anergic. When removed from the presence of the anergy-inducing stimulus, such cells regain responsiveness.

Immunoglobulins (Chapters 3–5)

Structure (Chapter 3)

The antigen-specific membrane receptors and secreted products of B cells are Ig molecules. Ig molecules are members of a large family of proteins designated the immunoglobulin supergene family. Members of the Ig supergene family have sequence homology, a common gene organization, and, where studied, similarities in three-dimensional structure. The latter is characterized by a structural element referred to as the Ig fold, generally consisting of a set of seven β-pleated sheets organized into two apposing layers (Fig. 5). Many of the cell surface proteins that participate in immunologic recognition processes, including the T-cell receptor (TCR), the CD3 complex, and molecules associated with the B-cell receptor (Igα and Igβ), are members of the Ig supergene family.

The Igs themselves are constructed of a unit that consists of two H chains and two L chains (Fig. 2). The H and L chains are composed of a series of domains, each consisting of approximately 110 amino acids.

The L chains, of which there are two types (κ and λ), consist of two domains. The carboxy-terminal domain is essentially identical among L chains of a given type and is referred to as the constant (C) region. As already discussed, the amino-terminal domain varies from L chain to L chain and contributes to the binding site of antibody. Because of its variability, it is referred to as the variable (V) region. The variability of this region is largely concentrated in three segments, designated the hypervariable or complementarity-determining regions (CDRs). The CDRs contain the amino acids that are the L chain's contribution to the lining of the antibody's combining site. The three CDRs are interspersed among four regions of much lower degree of variability, designated framework regions (FRs).

The H chains of Ig molecules are of several classes (μ, δ, γ [of which there are several subclasses], α, and ε). An assembled Ig molecule, consisting of one or more units of two identical H and L chains, derives its name from the H chain that it possesses. Thus, there are IgM, IgD, IgG, IgA, and IgE antibodies. The H chains each consist of a single amino-terminal V region and three or four C regions. In many H chains, a hinge region separates the first and second C regions and conveys flexibility to the molecule, allowing the two combining sites of a single unit to move in relation to one another so as to promote the binding of a single antibody molecule to an antigen that has more than one copy of the same epitope. Such divalent binding to a single antigenic structure results in a great gain in energy of interaction. The H-chain V region, like that of the L chain, contains three CDRs lining the combining site of the antibody and four FRs.

The C region of each H-chain class conveys unique functional attributes to the antibodies that possess it. Among the distinct biologic functions of each class of antibody are the following:

1. IgM antibodies are potent activators of the complement system (Chapter 29).
2. IgA antibodies are secreted into a variety of bodily fluids and are principally responsible for immunity at mucosal surfaces (Chapter 27).
3. IgE antibodies are bound by specific receptors (FcεRI) on basophils and mast cells. When cross-linked by antigen, these IgE/ FcεRI complexes cause the cells to release a set of mediators responsible for allergic inflammatory responses (Chapter 35).
4. IgD antibodies act virtually exclusively as membrane receptors for antigen.
5. IgG antibodies, made up of four subclasses in both humans and mice, mediate a wide range of functions including transplacental passage and opsonization of antigens through binding of antigen/antibody complexes to specialized Fc receptors on macrophages and other cell types.

IgD, IgG, and IgE antibodies consist of a single unit of two H and L chains. IgM antibodies are constructed of five or six such units, although they consist of a single unit when they act as membrane receptors. IgA antibodies may consist of one or more units. The antibodies that are made up of more than a single unit generally contain an additional polypeptide chain, the J chain, which plays an important role in the multiunit structure.

Each of the distinct Igs can exist as secreted antibodies and as membrane molecules. Antibodies and cell surface receptors of the same class made by a specific cell have identical structures except for differences in their carboxy-terminal regions. Membrane Ig possesses a hydrophobic region, spanning the membrane, and a short intracytoplasmic tail, both of which are lacking in the secretory form.

Immunoglobulin Genetics (Chapter 5)

The genetic makeup of the Ig H-chain gene has already been alluded to. The IgH chain gene of a mature lymphocyte is derived from a set of genetic elements that are separated from one another in the germline. The V region is composed of three types of genetic elements: V_H, D, and J_H. More than 100 V_H elements exist; there are more than 10 D elements and a small number of J_H elements (four in the mouse). An H-chain V_HDJ_H gene is created by the translocation of one of the D elements on a given chromosome to one of the J_H elements on that chromosome, generally with the excision of the intervening DNA. This is followed by a second translocation event in which one of the V_H elements is brought into apposition with the assembled DJ_H element to create the V_HDJ_H (V region) gene (Fig. 3). Although it is likely that the choice of the V_H, D, and J_H elements that are assembled is not entirely random, the combinatorial process allows the creation of a very large number of distinct H-chain V-region genes. Additional diversity is created by the junctional imprecision of the joining events and by the deletion of nucleotides and addition of new, untemplated nucleotides between D and J_H and between V_H and D, forming N regions in these areas. This further increases the diversity of distinct IgH chains that can be generated from the relatively modest amount of genetic information present in the germline.

The assembly of L-chain genes follows generally similar rules. However, L chains are assembled from V_L and J_L elements only. Although there is junctional diversity, no N regions exist for L chains. Additional diversity is provided by the existence of two classes of L chains, κ and λ.

An Ig molecule is assembled by the pairing of IgH-chain polypeptide with an IgL-chain polypeptide. Although this process is almost certainly not completely random, it allows the formation of an exceedingly large number of distinct Ig molecules, the majority of which will have individual specificities.

The rearrangement events that result in the assembly of expressible IgH and IgL chains occur in the course of B-cell development in pro-B cells and pre-B cells, respectively (Fig. 1). This process is regulated by the Ig products of the rearrangement events. The formation of a μ chain signals the termination of rearrangement of H-chain gene elements and the onset of rearrangement of L-chain gene elements, with κ rearrangements generally preceding λ rearrangements. One important consequence of this is that only a single expressible μ chain will be produced in a given cell, since the first expressible μ chain shuts off the possibility of producing an expressible μ chain on the alternative chromosome. Comparable mechanisms exist to ensure that only one L-chain gene is produced, leading to the phenomenon known as allelic exclusion. Thus, the product of only one of the two alternative allelic regions at both the H- and L-chain loci are expressed. The closely related phenomenon of L-chain isotype exclusion ensures the production of either κ or λ chains in an individual cell, but not both. An obvious but critical consequence of allelic exclusion is that an individual B cell makes antibodies, all of which have identical H- and L-chain V regions, a central prediction of the clonal selection theory of the immune response.

Class Switching (Chapter 24)

An individual B cell can continue to express the same IgH-chain V region but, as it matures, can switch the IgH-chain C region it uses (Fig. 3). Thus, a cell that expresses receptors of the IgM and IgD classes may differentiate into a cell that expresses IgG, IgA, or IgE receptors and then into a cell-secreting antibody of the same class as is expressed on the cell surface. This process allows the production of antibodies capable of mediating distinct biologic functions but that retain the same antigen-combining specificity. When linked with the process of affinity maturation of antibodies, Ig class switching provides antibodies of extremely high efficacy in preventing reinfection with microbial pathogens or in rapidly eliminating such pathogens. These two associated phenomena account for the high degree of effectiveness of antibodies produced in secondary immune responses.

The process of switching is known to involve a recombination event between specialized switch (S) regions, containing repetitive sequences, that are located upstream of each C region (with the exception of the δ C region). Thus, the S region upstream of the μ C_H region gene (Sμ) recombines with an S region upstream of a downstream isotype, such as Sγ1, to create a chimeric Sμ/Sγ1 region resulting in the deletion of the intervening DNA (Fig. 6). The genes encoding the C regions of the various γ chains (in the human γ1, γ2, γ3, and γ4; in the mouse γ1, γ2a, γ2b, and γ3), of the α chain and of the ε chain are located 3′ from the Cμ and Cδ genes.

The induction of the switching process is dependent on the action of a specialized set of B-cell stimulants. Of these, the most widely studied are bacterial lipopolysaccharide (LPS) and CD40L expressed on the surface of activated T cells. The targeting of the C